IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

GOUDSMIT ET AL.

Serial Number: 09/463,352 Group Art Unit: 1683

Filed: January 21, 2000 Examiner: B. Badio

For: NUCLEIC ACID SEQUENCES THAT CAN BE USED AS PRIMERS AND PROBES IN THE AMPLIFICATION AND DETECTION OF ALL SUBTYPES OF HIV-1

AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

December 19, 2000

Sir:

In response to the Office Action mailed July 20, 2000, please amend the above-identified application as follows. A Petition for a two-month extension of time and an Information Disclosure Statement accompany this response.

IN THE CLAIMS:

Please amend claims 4 - 8 as follows:

4. (twice amended) The pair of oligonucleotides according to claim 3, consisting of a first oligonucleotide [consisting essentially of] comprising the sequence of SEQ ID 9: aat tct aat acg act cac tat agg gAG AGG GGC GCC ACT GCT AGA GA and a second oligonucleotide [consisting essentially of] comprising the sequence of SEQ ID 5: CTC AAT AAA GCT TGC CTT GA

5. (twice amended) A method for the detection of HIV-1 nucleic acid in a sample [wherein the sample is subjected] ,comprising the steps of subjecting the sample to a nucleic acid amplification reaction under suitable conditions using a pair of oligonucleotides according to claim 1, and suitable amplification reagents [wherein] , and detecting the presence of [any] amplified HIV-1 nucleic acid [is detected].

6. (twice amended) The method according to claim 5, wherein the detection of [any] amplified HIV-1 nucleic acid is carried out by reacting the sample with one or more [oligonucleotides] oligonucleotide probes having [(a) sequence(s)] a sequence selected [form] from the group consisting of:
SEQ ID 6: TCT GGT AAC TAG AGA TCC CTC
SEQ ID 7: TAG TGT GTG CCC GTC TGT or
SEQ ID 8: AGT GTG TGC CCG TCT GTT,
one or more of which are provided with a detectable label, under suitable hybridization conditions, and detecting the presence of the label in any hybrids formed between the amplified [sequence] HIV-1 nucleic acid and the [probe] one or more probes.

7. (twice amended) The method according to claim 5, wherein the amplification [technique used] reaction is a transcription based amplification [technique] reaction.

8. (twice amended) A test kit for the detection of HIV-1 in a sample comprising:

a pair of [oligonucleitides] oligonucleotides according to claim 1;

one or more oligonucleotides comprising a nucleic acid sequence substantially complementary to at least part of the amplified nucleic acid sequence, provided with a detectable label; and

suitable amplification reagents.

Please add the following new claims 11 - 12:

11. A method for amplifying HIV-1 nucleic acid in a sample, comprising the step of subjecting the sample to a nucleic acid amplification reaction under suitable conditions using a pair of oligonucleotides according to claim 1, and suitable amplification reagents.

12. The method according to claim 11, wherein the amplification reaction is a transcription based amplification reaction.

REMARKS

In the Office Action mailed July 20, 2000, all the claims pending in the present application, claims 1 - 9, were rejected. Applicants respectfully request favorable reconsideration of the rejections and allowance of the present application in view of the above amendments and following remarks.

Applicants note the Examiner's mention that Applicant has not filed a certified copy of the PCT/EP98/04945 application as required by 35 USC 119(b). A certified copy of the PCT application should have been submitted to the Patent Office by the International Bureau, as occurs with all of the assignee's PCT national stage filings. Applicants ask that the Examiner call Applicants' representative to discuss the same, if necessary.

Claims 5 - 7 were rejected under 35 USC 112, second paragraph, as "incomplete for omitting essential steps," according to the Office Action. The Examiner listed the "omitted steps" a - c. This rejection is traversed in view of the above amendments and following remarks.

Claim 5 has been amended to recite in part that the sample

is subjected to a nucleic acid amplification reaction "under suitable conditions" using a pair of oligonucleotides according to claim 1. A skilled person in the art has available a number of known protocols and conditions for conducting amplification reactions. Furthermore, whether the desired sequence is amplified is not so much dependent on specific conditions, but rather on the use of specific primers, as defined by claim 1. The claimed method amplifies only the desired target sequence (HIV RNA) as a result of the selection of a pair of oligonucleotide primers according to claim 1. Additionally, the specification teaches on page 7, line 31, to page 8, line 1, that the annealing of the primers to the HIV genome defines the amplified target sequence, and further that the amplified sequence is located between the "primer-binding cites" within the LTR region of the HIV genome.

With respect to the Examiner's "omitted step" (c), the amplified nucleic acid in the present invention is usually not characterized according to its size, but rather according to its sequence by hybridizing the sequence with a complementary labeled probe. However, it would be clear to a person skilled in the art how to detect an amplified nucleic acid using a labeled probe, as stated above. Thus, the detection step of the amended claim 5 need not identify, for the purpose of clarity or definiteness, any specific detectable marker, as the Examiner stated in the "omitted step" (b).

Accordingly, Applicants request for the above reasons that the claim rejection under §112, second paragraph, be withdrawn.

Claims 1 - 9 were rejected under 35 USC 103(a) as unpatentable over McDonough et al. in view of Research Genetics. In general, the Examiner's position is that the Research Genetics reference enables the selection of primers for amplifying target HIV nucleic acid sequences, methods for which are known based on, for example, the cited McDonough reference. Specifically, the Examiner concluded on page 4 of the Office Action that the

artisan would have a reasonable expectation of success for reasons including that "the capacity to select any sequence [as a primer] had been reduced to the level of design choice." The §103 rejection is traversed for the following reasons.

The claimed primer pairs were not selected based on "design choice," but instead in a way the success of which would not have been reasonably expected (or obvious) based on the combination of the cited art.

The design program in Research Genetics is useful for finding, in a selected sequence, those sequences that fulfill the criteria designated by the user for the desired primers. The disclosed program is insufficient for identifying useful HIV primers, as defined by the claimed invention, for at least the following two reasons.

First, after selecting the target sequence, the skilled person using the program must still select from the large number of possible primers produced by the program. Then from all the possible primers, the skilled person must select preferred pairs of primers, as recited by the claimed invention.

Thus, the skilled person using the program would still be required to select the criteria desired for the primers produced from the program before and after using the program. Specifically, the program only identifies sequences as primers that fulfill the criteria inputted into the program by the user. For example, the user first must decide on the minimal and maximal lengths of the amplified sequence, the region from which the primer should be chosen, the minimal and maximal lengths of the primers, the range of melting temperatures that the user considers tolerable, and the GC content of the primers, etc. The program then generates only those primers fulfilling the criteria selected by the user. In contrast, the program cannot "predict" good and useful primer sequences, but rather can carry out only those selections that are inputted by the user.

The program thus identifies only those sequences fulfilling

the user's criteria. And the selected criteria obviously can vary. Thus, the output (in the form of primers) generated will not necessarily be a workable and useful solution -- especially when the primers are to be used as a diagnostic tool. When determining appropriate primers for HIV amplification, the primer should permit sensitive detection of the target sequence. Specifically, the primers should permit amplification even though the target sequence may be present only in minute amounts in the starting material. Indeed, a false negative test result will occur if a small amount of HIV genetic material goes undetected in the sample. The primers at the same time also should be highly specific, reacting only with the HIV target and thus eliminating the possibility of false positive test results.

Additionally, the primers should react with many different possible HIV isolates, since some sequence variation exists among different HIV isolates. The primers should be able to amplify nucleic acid from most if not all HIV variants; otherwise, HIV positive samples might go undetected, resulting in a false negative result.

Furthermore, such a program used in connection with the HIV genome can only select primers based on the specific target sequence inputted into the program, which in the case of HIV would be only those HIV sequence variants inputted by the user. The program provides no information to the user regarding the suitability of the generated primers for annealing to the sequences of other HIV variants. Moreover, the program is unable to predict or generate primers that can detect most if not all variants of HIV in a diagnostic test kit.

As stated above, the program only works based on the information inputted by the user. Specifically, the person skilled in the art must decide which part of the HIV genome contains a suitable target for amplification (from which primer sequences may be selected), as well as which HIV isolate should be used to select those primers. Furthermore, a skilled person

must decide how to manipulate those primers to have them anneal to as many HIV variants as possible, while still being selective enough to amplify only HIV derived sequences and nothing else. The program disclosed in Research Genetics provides no guidance in this respect.

Second, prior to Applicants' invention, primers described in the art for amplifying and/or quantitating HIV-1 RNA were located in the GAG or POL region of the genome. These regions were selected based on the knowledge of the p24 antigen assays and knowledge of the POL region being well conserved, respectively. The major drawback of these assays, however, was that they were unable to detect and quantify all group M and group O viruses known at the time of Applicants' invention. The primers of the present invention are not from the GAG region, but instead are from the long terminal repeat (LTR) of HIV-1.

In summary, even in the unlikely event that a skilled person designing a diagnostic kit would use the cited program to select HIV primers, the selection of those primers would depend on decisions made by the skilled person rather than as a result of features of the software program. The skilled person thus would be restricted by the program for at least the above reasons.

Accordingly, the combination of cited references relied on by the Examiner does not render obvious the claimed invention.

As additional evidence of nonobviousness, Applicants direct the Examiner's attention to the evidence of unexpected results of the claimed invention in the specification, including the evidence supporting the statement on the top of page 8 that "by using a pair of oligonucleotides according to the invention in an amplification reaction, accurate and reliable amplification of nucleic acid derived from all presently know[n] sub-types of HIV can be achieved." This statement is supported by Examples 2 - 5, which describe the most preferred primer pair of the invention (SEQ ID NO:1/SEQ ID NO:5, or SEQ ID NO:9/SEQ ID NO:5. SEQ ID NO:9 is SEQ ID NO:1 covalently bonded to an RNA polymerase promoter.")

Specifically, Example 5 shows that the preferred primer pair (SEQ ID NO:9/SEQ ID NO:5 (LTR)) along with a probe (SEQ ID NO:7) successfully detected HIV-1 RNA in 33/33 HIV-1 samples (which included cell culture supernatants from variants of group M subtypes A through H and variants from group O).

Accordingly, for these additional reasons, the cited combination of references fails to render obvious the claimed invention.

Applicants also submit herewith an Information Disclosure Statement. None of the references cited in the IDS appears to disclose or suggest the oligonucleotide pairs of Applicants' invention, or their use in the claimed methods.

In view of the foregoing, the present application is now in condition for allowance. Reconsideration and favorable action are earnestly solicited.

If any fees are due in this application, please charge our Deposit Account No. 02-2334.

Respectfully submitted,

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